MOLECULAR BIOLOGY AND BIOTECHNOLOGY

A Comprehensive Desk Reference

EDITED BY

Robert A. Meyers

EXHIBIT B

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Robert A. Meyers, Ph.D.
3715 Gleneagles Drive
Tarzana, CA 91356, USA

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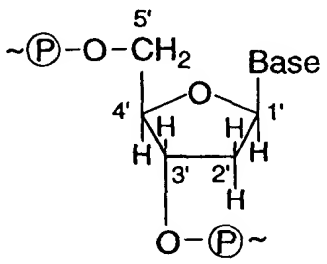
somewhat over strand breakage. A number of altered sugars re related to these processes have been identified, both in the nce and in the presence of oxygen. Based on detailed model es, the reactions and their kinetics leading to strand breakage absence of oxygen are fairly well understood. The primary s the abstraction of the H atom at C-4′:



is radical then eliminates a neighboring phosphate (linked to a gment of the DNA strand), leaving behind a radical cation that n react with water, either at the position that has eliminated the hosphate, or at C-4′. In the former case the other phosphate nction may be eliminated by the same mechanism; in double-anded DNA this sequence of events produces a clean gap in the ffected strand (the end groups of the two fragments are phosphate roups), with the loss of some information because of the disappear-nce of the damaged nucleoside. In the latter case the base is also ost, but additionally at the end of one of the fragment strands a maged sugar remains linked to the phosphate group—enzymati-lly speaking, it is a "dirty" end group. Details of the mechanism DNA strand breakage under conditions of oxygenation are less ell understood, but some of the relevant sugar lesions have been tected. Model systems (ribose 5-phosphate) indicate that under ese conditions C-5′ should be an additional site of attack and, nalogy, one would expect (no experimental evidence yet) the ′ peroxyl radical also to be a potential precursor for strand eakage.

So far, sugar damage has been discussed only in terms of OH dicals attacking this moiety. A contribution of the direct effect onization of the sugar moiety and the phosphate groups) must so be considered, but experimental evidence is not yet available. owever, there is another interesting aspect. In polynucleotides uch as poly(U) and poly(C), there is convincing evidence that ase radicals are the major precursors of the sugar radicals that ad to strand breakage and the release of an unmodified base at e site of the damaged sugar. It is less clear whether such a radical ansfer from the base to the sugar moiety can also occur in DNA.

In mammalian cells, DNA double-strand breaks are observed longside single-strand breaks approximately in the ratio of 1 : 25. his poses the question of how these double-strand breaks are rmed. It has been argued here that they result from clustered sions. In the literature, an additional one-hit route has been sug-sted that involves a radical transfer from the already broken and to the sugar moiety of the opposite strand, followed by eakage of this strand.

Carbon-centered radicals are known to add to the C=C bonds of cleobases. Such reactions, as well as radical–radical combination actions involving macroradicals, in principle allow the formation DNA–protein and DNA–DNA cross-links. In special cases, ch products have been observed with biological material, albeit ields considerably lower than DNA double-strand breaks.

See also DNA Damage and Repair; Free Radicals in Biochemistry and Medicine; Ultraviolet Radiation Damage to DNA.

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Isoenzymes

Adrian O. Vladutiu and Georgirene D. Vladutiu

Key Words

Antigenicity Property of some substances (mostly proteins) to elicit antibodies after introduction into a foreign (other than self) organism.

Electrophoresis Technique used to separate charged particles in solution, by the differences in their rates of migration in an applied electric field.

Epigenetic Modification of gene products by events or factors that occur after transcription and translation of the gene.

Fusion Protein Protein encoded for by a hybrid gene that has fused part of its original coding sequence with coding sequences of another gene for a different protein (e.g., a readily detected marker).

Locus Place on a chromosome occupied by a particular gene or its alleles.

Michaelis Constant The experimentally determined substrate concentration at which the enzymatic reaction proceeds at half its maximum velocity.

Ontogenic Development The course of the development of an organism from fertilization, through maturity, to death.

Phenotype The genetically and environmentally determined characteristics of an organism.

Polymorphism Occurrence in the same population of two or more alleles at a locus, with at least one allele having a frequency exceeding 1%.

Translation The formation of a peptide chain on the mRNA template from individual amino acids.